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Abstract

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Abstract: *DESCRIPTION (provided by applicant):* The natural breakdown of collagen is critical to physiological processes such as embryogenesis and bone remodeling. On the other hand, the destruction of collagen's triple-helical structure can also give rise to a variety of pathologies, including tumor cell spreading (metastasis), arthritis, glomerulonephritis, periodontal disease, and tissue ulcerations. Our laboratory has developed a target-based approach for profiling of extracellular matrix (ECM) degrading proteinases. More specifically, collagen-model conformationally constrained fluorescence resonance energy transfer (FRET) substrates have been utilized to quantify activities for collagenolytic matrix metalloproteinases (MMPs) and aggrecan-degrading members of the disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) family. These FRET substrate assays are fully compatible with multi-well formats. The specific aims for the present proposal are to (a) transfer the FRET substrate assays to the MLSCN for screening of collagenolytic MMP and aggrecandegrading ADAMTS family members that have been implicated in osteoarthritis (MMP-13 and ADAMTS-4) using the NIH Small Molecule Repository, and (b) verify and counter-screen inhibitor "hits" for MMP-13 and ADAMTS-4. Because the collagen-model FRET substrates have distinct conformational features that interact with the proteases' exosites, non-active site binding inhibitors can be identified that bind to MMPs and ADAMTSs. Exosites are secondary substrate binding sites, and have been shown to represent unique opportunities for the design of selective inhibitors. Our laboratory is uniquely positioned to utilize these HTS assays, based on our expertise with FRET triple-helical substrates for collagenolytic MMPs and FRET collagen-model substrates for aggrecanases. Initial clinical trials with MMP inhibitors were disappointing, with one of the problems being a lack of selectivity. In the case of aggrecanases, few inhibitors have been described. Selective inhibitors for MMP-13 and ADAMTS-4 would allow for a more definitive evaluation of these proteases in osteoarthritis, as well as representing a potential next generation in metalloproteinase therapeutics.

Thesaurus Terms: collagen, mbryogenesis, bone remodeling, metastasis, arthritis, glomerulonephritis, periodontal disease, tissue ulcerations, extracellular matrix (ECM)

degrading proteinases, fluorescence resonance energy transfer, FRET, collagenolytic matrix metalloproteinases, MMPs, aggrecan-degrading members of the disintegrin and metalloproteinase with thrombospondin, ADAMTS, Molecular Libraries Screening Centers Network, MLSCN, osteoarthritis, MMP-13, ADAMTS-4, NIH Small Molecule Repository, counter-screen, Exosites, High-throughput screening, HTS

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